

49. (Amended) The [compound] mixture of claim 48, wherein A and A' are independently proline or alanine residues.

50. (Amended) The [compound] mixture of claim 48, wherein m is an integer between 1 and 10.

51. (Amended) The [compound] mixture of claim 48, wherein m is 1.

Remarks

Claims 35, 37, 38, 39, 42, 44, 45, and 46 are amended as recommended by the Examiner to more particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The remaining claims are amended to provide proper reference to the antecedent term, "mixture."

No new matter has been added.

Withdrawn Rejections

Applicant gratefully acknowledges withdrawal of the rejection of claims under 37 C.F.R. 112(1), 102, and 103 over Metternich ('707) in view of the arguments filed 9/11/98.

Rejection Under 35 U.S.C. 112(2)

Claims 35, 37-39, 42, and 44-46 are rejected under 35 U.S.C. 112(2) "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". In particular, the Examiner objects to certain phrasing in reference to the "L-configuration" in the claims. The Examiner suggests language to clarify the meaning of the claims.

The claims are amended herewith to incorporate the changes suggested by the Examiner.

A description of the RS nomenclature system is provided below to facilitate the Examiner's review of the claims which may utilize this alternative nomenclature system.

The application describes "L-configuration" in reference to the boroproline compounds of the invention (page 7):

By 'the C bonded to B is in the L-configuration' is meant that the absolute configuration of C is like that of an L-amino acid. Thus, the $B(X_1)(X_2)$ group has the same relationship to the C as the $-COOH$ group of an L-amino acid has to its α carbon.

A more systematic method for classifying and naming stereo isomers is the absolute configuration of the four different substituents in the tetrahedron around the asymmetric carbon atom (e.g., the α carbon atom). To establish this system, a reference compound was selected (glyceraldehyde), which is the smallest sugar to have an asymmetric carbon atom. By convention in the art, the two stereo isomers of glyceraldehyde are designated L and D. Their absolute configurations have been established by x-ray analysis. The designations, L and D, also have been assigned to the amino acids by reference to the absolute configuration of glyceraldehyde. Thus, the stereo isomers of chiral compounds having a configuration related to that of L-glyceraldehyde are designed L, and the stereo isomers having a configuration related to D-glyceraldehyde are designated D. Thus, the symbols, L and D, refer to the absolute configuration of the four substituents around the chiral carbon. This is the nomenclature system which has been utilized in the pending application.

Most amino acids that are found in proteins can be unambiguously named using the D L system. However, compounds which have two or more chiral centers may be in 2^n possible stereo isomer configurations, where n is the number of chiral centers. These stereo isomers sometimes are designated using the RS system to more clearly specify the configurations of amino acids that contain two or more chiral centers. For example, compounds such as threonine isoleucine contain two asymmetric carbon atoms and therefore have four stereo isomer configurations. The isomers of compounds having two chiral centers are known as diastereomers. A complete discussion of the RS system of designating optical isomers for amino acids is provided in Principles in

In general, the RS system is designed to rank the four different substituent atoms around an asymmetric carbon atom in order of decreasing atomic number or in order of decreasing valence

density when the smallest or lowest-rank group is pointing directly away from the viewer. The different rankings are well known in the art (Lehninger, *supra*). If the decreasing rank order is seen to be clock-wise, the configuration around the chiral center is referred to as R; if the decreasing rank order is counter-clockwise, the configuration is referred to as S. Each chiral center is named accordingly using this system. Applying this system to threonine, one skilled in the art would determine that the designation, L-threonine, refers to (2S, 3R)-threonine in the RS system. The more traditional designations of L-, D-, L-allo, and D-allo, for threonine have been in common use for some time and continue to be used by those of skill in this art. However, the RS system increasingly is used to designate the amino acids, particularly those which contain more than one chiral center. Applicant believes that this brief explanation will facilitate the Examiner's review of any art which describes compounds in terms of the RS system.

Applicant has amended the claims as suggested by the examiner to include the phrase "the carbon atoms bearing boron are of the L-configuration". In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. 112(2).

Rejection of Claims 23 - 25 under 35 U.S.C. §103 in View of Bachovchin JBC

Claims 35-51 are rejected under 35 U.S.C. §103 as being unpatentable over the Bachovchin JBC reference (J. Biol. Chem. 265: 3738, 1990). The Examiner reiterates the basis for this rejection as stated in the prior Office Action and directs Applicant's attention to Bachovchin JBC Table I, page 3740, as depicting "several compounds falling within the scope of claim 35." In response to Applicant's prior arguments that the Bachovchin JBC reference did not *anticipate* the claimed invention because the reference *incorrectly* reported that the two peaks eluted from the silica gel column represented the separation of the D-isomer from the L-isomer, the Examiner states that "the presumption of enablement is conferred upon a statement contained within a scientific publication, even if that statement later turns out to be scientifically invalid" and that the claims "would have been obvious even without the reference to separation of the diastereomers."

Applicant argues that the Bachovchin JBC reference does not disclose or suggest

the art would have been motivated to separate the peptides containing L-boroPro from those containing D-boroPro isomer.

Claims 35-51 are pending. As amended herewith, each of claims 35-51 is directed to mixtures of the boroproline compounds and includes the limitation that "at least 96% of the carbon atoms bearing boron are of the L-configuration".

Applicant reiterates the arguments presented in response to the prior Office Action and, respectfully, traverses this rejection at least for the following additional reasons.

At the time the Bachovchin JBC reference was published, the person of ordinary skill would not have been motivated to develop an alternative method for separating the L and D-isomers because the Bachovchin JBC reference had reported that silica gel chromatography could be used for this purpose. Thus, there would have been no motivation for the person of ordinary skill in the art at the time the invention was made to attempt to develop an alternative separation method. As noted by the Examiner, the person of skill in the art would have regarded the Bachovchin JBC teaching of the separation method as a scientific fact. The fact that the silica gel chromatography method was inoperable for this purpose was only subsequently discovered by Dr. Bachovchin and was not known to the public at the time the invention was made. Absent this knowledge, there is no basis for a conclusion that one of ordinary skill in the art would have been motivated to develop an alternative method for separating the L and D-isomers. The evidence regarding the inoperability of the Bachovchin JBC separation method is provided in the Declaration of William Bachovchin, submitted herewith.

Dr. Bachovchin's declaration describes the events surrounding his discovery that he had "*incorrectly presumed* that one of the peaks collected following chromatography on silica gel represented an enriched fraction of the L-boro Pro isomer" (Bachovchin Decl. ¶6). At the time the silica gel chromatography was performed, Dr. Bachovchin did not suspect that Xaa-boroPro molecules could undergo a cis-trans conformational equilibrium on a slow time scale and that the cis and trans isomeric forms could account for the different fractions eluted from the silica gel column (Bachovchin Decl. ¶7). Dr. Bachovchin has since established that all Xaa-boroPro molecules undergo this conformational equilibration and that the cis isomer is inactive, the trans is

several Xaa-boroPro molecules (i.e., cis and trans L, L and L, D enantiomers) (Bachovchin Decl. ¶8).

The Bachovchin JBC reference includes results which prove that Dr. Flentke had a mixture of the L,L. and L,D enantiomers, in the trans forms (Bachovchin Decl. ¶8). For example, the resonance reported at 3.1 ppm, the "a" proton of the proline ring, is diagnostic of the trans isomers (Bachovchin Decl. ¶8). The cis or cyclic form would have shown this proton resonating at 2.6 ppm (Bachovchin Decl. ¶8). Such a signal is not present in Dr. Flentke's spectra of the early eluting fractions, but is present in the late running fractions, thereby establishing that he had indeed effected a separation of trans from cis and that this explains the relative activities of the two fractions (Bachovchin Decl. ¶8).

That Dr. Flentke's early eluate contained both L,L. and L,D isomers also is demonstrated by the poor resolution of several of the NMR signals (Bachovchin Decl. ¶9). In particular, Bachovchin JBC makes reference to a multiplet at 3.5 to 3.6 ppm (Bachovchin Decl. ¶9). These are the proline ring protons in the d position (Bachovchin Decl. ¶9). In bone-fide L, L enantiomer, these two protons are clearly resolved, one at 3.46 ppm, the second at 3.6 ppm as shown in (Bachovchin Decl. Exhibit C). The reason Dr. Flentke was not able to resolve the two signals at 3.46 ppm and 3.6 ppm is that the corresponding L,D enantiomer was giving rise to signals with similar chemical shifts, though different enough to prevent resolution of the individual signals (Bachovchin Decl. ¶9).

Bachovchin JBC also makes reference to a multiplet at 4.3 ppm, again revealing the presence of overlapping signals (Bachovchin Decl. ¶11). The spectra of the pure L,L. enantiomer, in contrast, shows a clearly resolved quartet for this proton (see Bachovchin Decl. Exhibit C).

Bachovchin JBC also makes reference to a multiplet at 3.1 ppm, again revealing the presence of overlapping signals (Bachovchin Decl. ¶12). The spectra of the pure L,L. enantiomer, in contrast, shows a clearly resolved doublet of doublets for this proton (see Bachovchin Decl. Exhibit C).

In view of the evidence submitted herewith and described above, Dr. Bachovchin concluded that the "early" and "later" fractions described in Bachovchin JBC do not represent the

fully appreciate the multiple forms (e.g., geometric isomers, optical isomers, intramolecular reaction products) in which the dipeptides could exist (Bachovchin Decl. ¶14). These multiple

forms were subsequently discovered and described in a later Biochemistry 1993 reference: W. Gutheil and W. Bachovchin, "Separation of L-Pro-DL-boroPro into Its Component Diastereomers and Kinetic Analysis of Their Inhibition of Dipeptidyl Peptidase IV. A New Method for the Analysis of Slow, Tight-Binding Inhibition", Biochemistry 32: (1993) (attached to the Bachovchin Decl. as Exhibit D).

The Biochemistry 1993 reference describes the preparation of L, L and L, D Pro-boroPro Diastereomers by C18 HPLC using separation conditions which are substantially identical to the HPLC separation conditions provided in the above-identified patent application (Bachovchin Decl. ¶15). Dr. Bachovchin ultimately *abandoned silica gel chromatography* as an approach for purifying the enantiomers and, instead, developed the alternative reverse phase technique (the C18 separation described in the above-identified patent application) to separate the purified L, L-isomers (Bachovchin Decl. ¶16).

The case law is clear that "obvious-to-try" is not the proper legal standard for determining nonobviousness. Nonobviousness will be found only (1) when the subject matter of a claimed invention would have been "obvious-to-try," and (2) when one of ordinary skill in the art would have had a reasonable expectation that the subject matter of the claimed invention would succeed. In the present case, even assuming *arguendo* that the claimed invention was "obvious to try" the requisite "reasonable expectation of success" is absent. There is no suggestion in Bachovchin JBC of any method other than silica gel chromatography to separate the L and D-isomers of the boroproline compounds. Even Dr. Bachovchin, the named inventor of the above-identified patent application admits that his assumptions about the utility of silica gel chromatography for separating these isomers were *incorrect* and that his development of a successful separation technique was not developed and reported in the literature until three years later in the Biochemistry 1993 reference. In view of this evidence, at the time the invention was made, the person of ordinary skill would not have been motivated to develop an alternative method to silica gel chromatography and, even if motivated, the person of ordinary skill would not have had the suggest otherwise.

In view of the foregoing evidence, Applicant respectfully requests that the Examiner

reconsider and withdraw the rejection of claims under 35 U.S.C. 103 as obvious in view of the Bachovchin JBC reference.

Rejection of Claims under 35 U.S.C. 103 in view of Bachovchin '493

Claims 35-51 are rejected under 35 U.S.C. 103 as being unpatentable over Bachovchin (USP 4,935,493). According to the Examiner, Bachovchin '493 "does not teach that the "all-L" peptide should be isolated"; however, the Examiner takes the position that "one of ordinary skill would have been motivated to isolate the "all-L" peptide, since peptides consisting of only L-amino acids are those that are naturally occurring". The Examiner concludes that the claimed invention is obvious in view of this reference.

Applicant respectfully traverses this rejection for the reasons set forth above. Bachovchin '493 does not describe a preparation containing a mixture of isomers that is enriched in the L-isomer as claimed in the pending claims, nor does this reference suggest any method for separating a mixture of stereoisomers to obtain the claimed mixture.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. 103 as obvious in view of the Bachovchin '493 patent.

**Rejection of Claims Under 35 U.S.C. §103 in view of
Bachovchin (WO 89/03223) or Flentke (PNAS 88:1556 (1991))**

Claims 35-51 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (WO 89/03223) or Flentke (PNAS 88:1556 (1991)) for the reasons of record and as set forth above.

Bachovchin WO 89/03223 does not teach or suggest the purification of an L-isomer. Rather, this Bachovchin PCT publication suggests separating the isomers using a silica gel column as described in Bachovchin JBC. Accordingly, the Bachovchin WO 89/03223 publication does not teach, suggest or render obvious the invention as now claimed at least for the same reasons set forth above.

THE REJECTION OF CLAIMS 35-51 UNDER 35 U.S.C. §103 AS BEING UNPATENTABLE OVER BACHOVCHIN (WO 89/03223) OR FLENTKE (PNAS 88:1556 (1991))

presented above are reiterated hereinafter, this reference now does not teach or suggest a method which is obvious the invention of claims 35-51.

In summary, there is nothing in the Bachovchin WO89/03223 publication or the Flentke PNAS reference to suggest the isolation of the various isomers that may be present in the preparation or to suggest a method for separating these isomers. Thus, even if the person of ordinary skill in the art had been motivated to further purify the various isomers of the claimed compounds (which Applicant disputes), there is no knowledge in the art cited by the Examiner to suggest how to accomplish this objective. It was not until Applicant discovered the enhanced activity and was able to correlate the enhanced activity to the claimed isomeric form that the person of ordinary skill would have been motivated to develop methods to purify said compounds.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and find claims 35- 51 patentable over the Bachovchin WO 89/03223 and Flentke PNAS references.

Information Disclosure Statement Comments

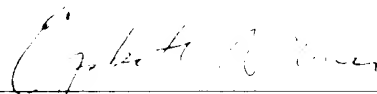
The Examiner previously indicated certain deficiencies in the Information Disclosure Statement, e.g., incomplete citations and ambiguity as to whether the complete reference or a part of the reference had been provided. In view of the Examiner's comments, a revised Information Disclosure Statement 1449 list will be submitted. Applicant respectfully requests that the Examiner make the cited art of record.

Summary

Applicants wish to expedite the prosecution of this application. Accordingly, if the Examiner feels that a telephone conference would be helpful, he is respectfully requested to call the undersigned attorney at the telephone number presented below.

It is believed that the rejections of record are not applicable to the pending claims. Accordingly, it is respectfully requested that favorable action on the new claims be taken.

Respectfully submitted,



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